UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,870	09/05/2003	George D. Purvis III	016939.0103 (03-52279-FAI	7307

5073 7590 07/31/2009
BAKER BOTTS L.L.P.
2001 ROSS AVENUE
SUITE 600
DALLAS, TX 75201-2980

EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
07/31/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ptomail1@bakerbotts.com
glenda.orrantia@bakerbotts.com

Office Action Summary	Application No.	Applicant(s)
	10/655,870	PURVIS, GEORGE D.
	Examiner	**Art Unit**
	John S. Brusca	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9-11,19-21 and 29-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9-11,19-21 and 29-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1,9-11, 19-21, and 29-43 are pending.

Claims 1,9-11, 19-21, and 29-43 are rejected.

Claim Rejections - 35 USC § 101

2. The rejection of claims 21, 29, and 30 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter in the Office action mailed 26 February 2009 is withdrawn in view of the amendment to the claims filed 22 May 2009.

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 11, 19, 20, and 36-39 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. This rejection is maintained from the Office action mailed 26 February 2009 and extended to new claims 36-39.

Claims 11, 19, 20, and 36-39 are drawn to a process. A process is statutory subject matter under 35 U.S.C. 101 if: (1) it is tied to a particular machine or apparatus or (2) it transforms an article to a different state or thing (In re Bilski, 88 USPQ2d 1385 Fed. Cir. 2008).

The claimed subject matter is not limited to a particular apparatus or machine. The claimed subject matter requires calculation of repulsion terms, potential of mean force terms, and other calculation steps of comparison of protein structure data. None of the steps are limited to require use of a computer, and all steps could be performed mentally or manually. The applicants have amended the claims to require that a computer system is used while performing the claimed

process, however a computer system could be a program per se that could be used by a computer. To qualify as a statutory process, the claims should require use of a machine within the steps of the claimed subject matter or require transformation of an article to a different state or thing. Insignificant extra-solution activity in the claimed subject matter will not be considered sufficient to convert a process that otherwise recites only mental steps into statutory subject matter (In re Grams 12 USPQ2d 1824 Fed. Cir. 1989). Preamble limitations that require the claimed process to comprise machine implemented steps will not be considered sufficient to convert a process that otherwise recites only mental steps into statutory subject matter. The applicants are cautioned against introduction of new matter in an amendment.

The rejection would be overcome by requiring that the process is performed on a computer.

Claim Rejections - 35 USC § 112

5. The rejection of claims 21, 22, 25, 27, 29, and 30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement in the Office action mailed 26 February 2009 is withdrawn in view of the amendment to the claims filed 22 May 2009.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1,9-11, 19-21, and 29-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite for the recitation in independent claims 1, 11, 21, and 31 the phrase “the atom-pair type being defined by the first and second elements and the combination of

local bonding environments" because it is not clear what effect the local bonding environments have on the subsequent determinations of minimum binding-energy distance values and well-depth values. The claimed subject matter does not explicitly require use of bonding environment information. For the purpose of examination, the claimed subject matter has been assumed to require consideration of the effect of bonding environments when determining the minimum binding-energy distance values and well-depth values of atom-pairs.

Claim Rejections - 35 USC § 103

8. The rejection of claims 1, 9, 11, 19, 21, 29, and 31 under 35 U.S.C. 103(a) as being unpatentable over Muegge et al. (Muegge I) in view of Mitchell et al. in view of Muegge et al. (Muegge II) in the Office action mailed 26 February 2009 is withdrawn in view of the amendment to the claims filed 22 May 2009.

9. The rejection of claims 1, 9, 10, 11, 19, 20, 21, 29, and 30 under 35 U.S.C. 103(a) as being unpatentable over Muegge et al. (Muegge I) in view of Mitchell et al. in view of Muegge et al. (Muegge II) as applied to claims 1, 9, 11, 19, 21, 29, and 31 above and further in view of Morris et al. in the Office action mailed 26 February 2009 is withdrawn in view of the amendment to the claims filed 22 May 2009.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 9, 11, 19, 21, 29, and 31-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muegge et al. (Muegge I) (J. Med. Chem. Vol. 42, pages 2498-2503 (1999),

reference G in the IDS filed 07 April 2004) in view of Mitchell et al. (J. Comput. Chem. Vol. 20, pages 1165-1176 (1999), reference U in the notice of references cited mailed 07 March 2006) in view of Muegge et al. (Muegge II) (Med. Chem. Res. Vol. 9, pages 490-500 (1999), reference F in the IDS filed 07 April 2004) in view of Oprea et al. (Perspectives in Drug Discovery and Design, Vol. 9-11, pages 35-61 (1998)) in view of Lehninger (Biochemistry Second Edition (1975)).

The claims are drawn to methods and apparatus therefor for computing a potential of mean force (PMF) scores of a protein-ligand complex from an empirically derived minimum binding-energy distances and well-depth values for each atom-pair analyzed. The atom-pair type is defined by the two atoms and a combination of local bonding environments selected from polar or non polar aliphatic, polar or nonpolar aromatic, or hydrogen bond donor or acceptor. In one embodiment claimed subject matter requires considering the effect of bonding environments when determining the minimum binding-energy distance values and well-depth values of atom-pairs. A PMF score of the protein-ligand complex is calculated from each atom-pair that is analyzed, and a structure of the protein-ligand complex is calculated from each PMF score of the protein-ligand complex. The calculated protein-ligand complex structure is compared to an actual analyzed structure of the protein-ligand complex. The extent of agreement between root mean square values of the protein-ligand complexes is used as a measure of the quality of the PMF score. The PMF score of an atom-pair that best agrees with data of the actual analyzed protein ligand-complex is outputted to a user. In some embodiments the empirically derived minimum binding-energy distances and well-depth values are the product of a manual or automatic process. In some embodiments the process is iterated.

Muegge I shows especially on page 2499 a method and apparatus for calculation of a PMF of a protein-ligand complex by determining the PMF of each atom pair of the complex. Muegge I shows on page 2499 that consideration of the van der Waals interactions at short distances is beneficial for determination of the PMF of an atom pair because without such corrections for the short distance repulsion of van der Waals interactions the PMF value would be infinity at short distances. Muegge I shows that if the van der Waals term is larger than 4 kcal/mol, the PMF is overwritten by the van der Waals term value.

Muegge I does not show explicitly sets of empirical data used to derive the PMF of an atom pair or use of empirical data that best agrees with data of an actual analyzed structure of a protein-ligand complex. Muegge I does not show use of the extent of agreement between root mean square values of the protein-ligand complexes as a measure of the quality of the PMF score. Muegge I does not show considering the effect of bonding environments when determining the minimum binding-energy distance values and well-depth values of atom-pairs.

Mitchell et al. shows in the abstract and throughout a method and apparatus for calculation of a PMF score of a protein ligand complex by determining the PMF of each atom pair of the complex. Mitchell et al. shows use of data from the Brookhaven Protein Databank on page 1167, and throughout to aid in determining PMF of atom pairs of interest.

Muegge II shows in the abstract and throughout a method and apparatus for calculation of a PMF score of a protein ligand complex by determining the PMF of each atom pair of the complex. Muegge II shows comparison of root mean square deviations of multiple ligands on pages 492- 497.

Oprea et al. reviews scoring functions for predicting the binding affinity of a ligand to a protein receptor. The LUDI scoring function takes into account hydrogen bonding and hydrophobic complementarity (pages 39-40). The Wallqvist scoring function determines inter-atomic contact preferences (pages 40-41). The Verkhivker scoring function determines inter-atomic distances by taking into account interaction between polar and nonpolar groups. VALIDATE takes into account physico-chemical properties of both the ligand and the receptor including electrostatic interaction, and hydrophilic and polar complementarity (pages 43-51). The Jain scoring function takes into account polarity, repulsion, hydrogen bonds, salt bridges, and salvation (pages 51-53). The HTS approach outlined on pages 54-55 also takes into account hydrogen bonds and polarity to determine distances between atoms of ligands and protein receptors.

Lehninger shows in figures 4-2 through 4-4 that the amino acids that are the constituents of proteins comprise amino acids that are nonpolar aliphatic (e.g., alanine, valine leucine, isoleucine), nonpolar aromatic (e.g., phenylalanine, trypytophan), and polar aliphatic (e.g., glycine, serine, threonine), and polar aromatic (e.g., tyrosine).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the empirical data of Mitchell et al. to aid in determining the PMF values of Muegge I because Mitchell et al. shows use of empirical data in determining PMF values. It would have been further obvious to use empirical data that best agreed with the protein ligand under examination to improve accuracy of the method. It would have been further obvious to consider the root mean square deviations of data used in the method of Muegge II to perform the comparisons because Muegge II shows that comparison of root mean square deviations is a

useful method to compare structures. It would have been further obvious to take into account the bonding environment of the atom-pair because Oprea et al. show numerous scoring functions for docking ligands and receptor proteins that take into account the bonding environment, including hydrogen bonding, and Lehninger shows that proteins comprise amino acids with polar and nonpolar aliphatic groups and polar and nonpolar aromatic groups. It would have been further obvious to iterate the method as needed to determine the values of all atom-pairs formed between a ligand and a receptor.

12. Claims 1, 9, 10, 11, 19, 20, 21, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muegge et al. (Muegge I) in view of Mitchell et al. in view of Muegge et al. (Muegge II) in view of Oprea et al. in view of Lehninger further in view of Morris et al. (J. Computational Chemistry Vol. 19, pages 1639-1662 (1998)).

The claims are drawn to a method and apparatus of determining a PMF score for a protein ligand complex in which data used to generate a PMF of atom pairs in the complex is determined by a genetic algorithm.

Muegge et al. (Muegge I) in view of Mitchell et al. in view of Muegge et al. (Muegge II) in view of Oprea et al. in view of Lehninger as applied to claims 1, 9, 11, 19, 21, 29, and 31-43 above does not show data used to generate a PMF of atom pairs in the complex determined by a genetic algorithm.

Morris et al. discloses methods of using genetic algorithms in docking programs to predict bound conformations of flexible ligands. Morris et al discuss the known methods of three dimensional protein-ligand analysis, which include the automated determination of minimized free energy conformations. Morris et al. discusses known genetic algorithms (page

1641), and their use in docking programs. The genetic algorithm is used for searching the global computational space to identify a most fit structure of the protein-ligand interaction. The AUTODOCK program performs a specified number of dockings, then carries out conformational cluster analysis on the docked conformations to determine which are similar ranked by increasing energy. The "fitness" of the structure can be based on a variety of parameters. AUTODOCK uses a dispersion/repulsion term, a hydrogen bonding term, and a screened Coulombic electrostatic potential. MSMS is used to compute the analytical molecular surfaces, which is analogous to a well-depth value. Morris et al. show that their combination of a genetic algorithm, free energy calculations, and docking/design programs provide faster and more reliable results.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the known computation methods of genetic algorithms to the methods of Muegge et al. (Muegge I) in view of Mitchell et al. in view of Muegge et al. (Muegge II) in view of Oprea et al. in view of Lehninger as applied to claims 1, 9, 11, 19, 21, 29, and 31-43 above for scoring PMF functions of protein-ligand interactions because Morris et al. shows that genetic algorithms provide faster and more successful searching of free energy conformations.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John S. Brusca/
Primary Examiner, Art Unit 1631

jsb